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EXAMINER	
RAWLINGS, STEPHEN L	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/357,704	BANDER, NEIL H.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-74,76-79,124-127,129,130,137-148,150-168,170-172,186 and 190* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-74,76-79,124-127,129,130,137-148,150-168,170-172,186 and 190* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20070723*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed July 19, 2007, is acknowledged and has been entered. Claims 75, 80, 136, 149, 169, and 173 have been canceled. Claims 69, 79, 124-127, 129, 130, 137, 156, 172, 186, and 190 have been amended.

2. Receipt of the declaration of availability by Laurie Butler Lawrence filed July 19, 2007, is acknowledged.

3. Claims 69-74, 76-79, 124-127, 129, 130, 137-148, 150-168, 170-172, 186, and 190 are pending in the application and are currently subject to examination.

Information Disclosure Statement

4. The information disclosure filed July 19, 2007, has been considered. An initialed copy is enclosed.

Terminal Disclaimer

5. The terminal disclaimer filed on July 19, 2007, disclaiming the terminal portion of any patent granted on this application, which would extend beyond the expiration date of U.S. Patent No. 6,136,311 A has been reviewed and is accepted. The terminal disclaimer has been recorded.

Priority

6. Applicant's claim under 35 USC § 120 for benefit of the earlier filing date of the U.S. Patent Application No. 08/838,682, filed April 9, 1997, which claims benefit of U.S. Provisional Application No. 60/022,125, filed July 18, 1996, and U.S. Provisional Application No. 60/016,976, filed May 6, 1996, is acknowledged.

However, claims 69-74, 76-79, 124-127, 129, 130, 137-148, 150-168, 170-172, 186, and 190 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of claims 69-74, 76-79, 124-127, 129, 130, 137-148, 150-168, 170-172, 186, and 190 is deemed the filing date of the instant application, namely July 20, 1999.

Grounds of Objection and Rejection Withdrawn

7. Unless specifically reiterated below, Applicant's amendment and/or arguments submitted as part of the papers filed July 19, 2007, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed January 19, 2007.

Grounds of Objection and Rejection Maintained

Claims

8. The objection to claims 79 and 172 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, is maintained.

At pages 13 and 14 of the amendment filed July 19, 2007, Applicant has traversed the propriety of maintaining this ground of objection, arguing that it is clear that monoclonal antibody J415 competes for binding to PSMA with itself.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claim 79 is drawn in the alternative to an invention selected from the following:

(a) The method of claim 78, wherein the antibody is monoclonal antibody E99 (i.e., the monoclonal antibody produced by the deposited hybridoma of ATCC accession number HB-12101);

(b) The method of claim 78, wherein the antibody is monoclonal antibody J415 (i.e., the monoclonal antibody produced by the deposited hybridoma of ATCC accession number HB-12109);

(c) The method of claim 78, wherein the antibody is monoclonal antibody J533 (i.e., the monoclonal antibody produced by the deposited hybridoma of ATCC accession number HB-12127); and

(d) The method of claim 78, wherein the antibody is monoclonal antibody J591 (i.e., the monoclonal antibody produced by the deposited hybridoma of ATCC accession number HB-12126).

Claim 78 is drawn to the method of claim 69, wherein the antibody is a monoclonal antibody or a polyclonal antibody; and claim 69 is drawn to a method of treating prostate cancer comprising providing and administering to a subject an antibody or antigen binding portion that binds to prostate specific membrane antigen (PSMA) and competes for binding to PSMA with a monoclonal antibody selected from the group consisting of monoclonal antibody E99, monoclonal antibody J415, monoclonal antibody J533, and monoclonal antibody J591.

As previously explained, the specification describes monoclonal antibodies E99, J533, and J591 monoclonal antibody as recognizing to "competing binding sites" of PSMA (i.e., they presumably bind to same, or an overlapping epitope of PSMA, so as to compete with one another for binding to PSMA); see, e.g., page 38, lines 11-16. However, the specification describes the fourth monoclonal antibody, namely J415, as recognizing a "non-competing binding site" of PSMA (i.e., monoclonal antibody J415 likely binds to a distinct epitope of PSMA not recognized by any of monoclonal antibodies E99, J533, and J591).

Applicant has argued that an antibody competes with itself for binding; agreeably a molecule of any given ligand is fully expected to compete for binding to its receptor with any other molecule of the same ligand. but it is not evident that Applicant contemplated as their invention a method of treating prostate cancer comprising administering to a subject an antibody or antigen binding portion thereof that binds to PSMA and competes for binding to PSMA *with itself.* Rather, it is submitted that the specification would suggest that Applicant must have contemplated such a method comprising administering to the subject *another* antibody or antigen binding portion thereof that binds to PSMA and competes for binding to PSMA with a

monoclonal antibody selected from the group consisting of monoclonal antibodies E99, J533, J591, and J415, the latter of which is described with particularity therein.

Monoclonal antibody J415 does not compete for binding to PSMA with any of monoclonal antibodies E99, J533, and J591; moreover, none of monoclonal antibodies E99, J533, and J591 compete for binding to PSMA with monoclonal antibody J415. In fact, as further commented upon below, no other monoclonal antibody that binds to PSMA, which is capable of competing for binding to PSMA with monoclonal antibody J415, is described in the specification with any degree of particularity that might reasonably suggest that Applicant had, at the time this application was filed, possession of such a genus of antibodies capable of competing for binding to PSMA with monoclonal antibody J415, the antibody *itself* sensibly excluded[1].

Therefore, insofar as claim 79 is drawn to the method of claim 78, wherein the antibody is monoclonal antibody E99, monoclonal antibody J533, or monoclonal antibody J591, it is aptly noted that claim 79 properly limits the preceding claims, provided that claim 69 is drawn to any one of the methods comprising administering to a subject an antibody or antigen binding portion thereof that binds to PSMA and competes for binding to PSMA with a monoclonal antibody selected from any one of these same three monoclonal antibodies, because each competes with the others. However, insofar as claim 79 is drawn to the method of claim 78, wherein the antibody is a J415 monoclonal antibody, it fails to properly limit the subject matter of the preceding claims drawn to any one of the methods comprising administering to a subject an antibody or antigen binding portion thereof that binds to PSMA and competes for binding to PSMA with a monoclonal antibody selected from monoclonal antibody E99, monoclonal antibody J533, or monoclonal antibody J591 because monoclonal antibody J415 does not compete for binding with any of these three antibodies.

Again, Applicant is reminded that to properly limit the subject matter of a preceding claim, a dependent claim must limit *each* embodiment of the preceding claim, or must be written in a manner that makes evident that it is directed to only those embodiments of the preceding claim, which are further limited by its recitation.

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[1] In selecting from among a plurality of antibodies an antibody capable of competing for binding to an antigen with a given species of antibody, it would be useless to select this same species of antibody,

Claim 172 fails to properly further limit the subject matter of claim 126 for the reason claim 79 fails to properly further limit the subject matter of preceding claims 69 and 78, which is provided in the paragraph above.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or otherwise amend the claims so as to remedy this issue.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. The rejection of claims 69-74, 76-78, 124-127, 129, 130, 137-148, 150-168, 170, 171, 186, and 190 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained.

Beginning at page 14 of the amendment filed July 19, 2007, Applicant has traversed the propriety of maintaining this ground of objection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claims 79 and 172, which are not rejected herein, are directed to a monoclonal antibody selected from the group consisting of monoclonal antibody E99, monoclonal antibody J415, monoclonal antibody J533, and monoclonal antibody J591.

However, claims 69-74, 76-79, 124-127, 129, 130, 137-148, 150-168, 170-172, 186, and 190 are directed to a genus of antibodies or antigen-binding fragments thereof, which bind to PSMA and compete for binding to PSMA with a monoclonal antibody selected from the group consisting of monoclonal antibody E99, monoclonal antibody J415, monoclonal antibody J533, and monoclonal antibody J591.

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which is already possessed, particularly where it would be clear that the objective is to identify another antibody having this functional capability, not the antibody itself.

As previously explained, the claims are indefinite because of the recitation in claim 69, for example, of "which competes for binding to PSMA with a monoclonal antibody" selected from the specified group of monoclonal antibodies.

At page 27, lines 33-35, for example, of the specification discloses: "Whether two biological agents bind to competing or non-competing binding sites can be determined by conventional competitive binding assays". The specification describes the binding assay, which was used to determine, allegedly, whether monoclonal antibodies J591, J533, E99, and J415 detect the same or different epitopes; see, e.g., page 37, line 23, through page 38, line 25. As explained at page 38, lines 5-10, the controls used as the basis for this determination consisted of using the same monoclonal antibody both cold and labeled to define "100% competition", or using monoclonal antibody to a totally different molecule (e.g., monoclonal antibody I-56, which detects inhibin) to define "0% competition". Thus, according to these disclosures, it is evident that one determines whether an antibody "competes" for binding to PSMA with one of the selected antibodies by measuring the percentage of binding of a detectably labeled antibody in the presence of an unlabeled (i.e., "cold") antibody.

Nevertheless, it is aptly noted that the term "competes" is not expressly defined in the specification, so it may not be immediately clear what functional attribute characterizes the claimed antibody or antigen binding fragment thereof; moreover, as discussed in greater detail below, the degree to which the claimed antibody "competes" for binding to PSMA with any one of the recited monoclonal antibodies, nor the methodology used to make the determination, and the conditions under which that determination are made, are not delineated by the claims and are not ascertainable from the disclosure.

The term "competition" is defined, for example, by Stedman's Online Medical Dictionary, 27th Edition as meaning: "The process by which the activity or presence of one substance interferes with, or suppresses, the activity of another substance with similar affinities" (Copyright © 2006 Lippincott Williams & Wilkins). Given this definition, the claims are directed to antibodies or antigen-binding fragments thereof that interfere with, or suppress binding of one of the selected monoclonal antibodies to PSMA, as perhaps determined using the exemplified binding assay.

This interpretation is not inconsistent with the specification, which at page 38, lines 11-13, for example, discloses: "The results indicated that J591, J533, and E99 each **interfere, compete, or block** binding of one another but do not block binding of J415 and vice versa" (emboldened for emphasis).

Thus, while one may know how to determine whether an antibody "competes" with one of the selected monoclonal antibodies, it is apparent that the degree to which an antibody competes with another antibody is a relative or subjective expression, and the requisite degree to which the claimed antibody competes with any of the selected monoclonal antibodies cannot be ascertained from the disclosure.

Contrary to the assertion in the specification that such a binding assay determines whether two antibodies bind to the same antigenic determinant (i.e., epitope), competing antibodies do not necessarily bind the same epitopes. For example, "competing" antibodies may bind spatially overlapping but discrete epitopes. Simply because two antibodies cannot simultaneously occupy the same space, such an antibody, once bound to the antigen, sterically hinders or blocks binding of another such antibody. As another example, a "competing" antibody might not necessarily bind to the same epitope of an antigen as another antibody, if one of the antibodies induces conformational shifts in the three-dimensional structure of the antigen upon binding, which prevents binding of the other antibody to the antigen because the epitope to which it would otherwise bind is unrecognizable as a consequence of the structural change.

In addition, it is recognized that the degree of binding of an antibody, which is observed in the exemplified competitive binding assay, will depend upon the concentration of the detectably labeled antibody and the unlabeled competing antibody. Typically, the higher the concentration of the unlabeled competitor, the lower the percentage of binding of the labeled antibody. So, at *high enough* concentrations, any antibody might be deemed capable of "competing" for binding to an antigen with any other antibody, regardless of whether or not the different antibodies bind to the same, or even overlapping epitopes.

George et al. (*Circulation.* 1998; **97**: 900-906), for example, describes different antibodies, which do not bind to the same epitope of an antigen, but are nevertheless capable of competing with one another for binding to the antigen; see entire document (e.g., page 903, paragraph bridging columns 1 and 2). More particularly, George et al. describes three

antibodies, which bind decidedly different, non-cross-reactive epitopes on β2GPI; yet, George et al. teaches each is able to "compete" *to some extent* with any of the others for binding to the antigen (page 903, paragraph bridging columns 1 and 2). For example, George et al. teaches monoclonal antibody ILA-4 competed with itself for binding to the antigen (% inhibition = 90 ± 11% at competitor antibody concentrations of 30 μg/ml), but George et al. discloses, despite its binding a non-overlapping epitope, monoclonal antibody ILA-1 also "competed", albeit perhaps unsubstantially with monoclonal antibody ILA-4 for binding to the antigen (% inhibition = 9 ± 4%).

Accordingly, George et al. illustrates the capricious and arbitrary nature of determinations that different antibodies bind to the same or different epitopes, which are based upon the results of competitive binding assays, such as the assay exemplified in the specification. Although each of the described antibodies "competed" to a measurable extent with the other antibodies for binding to the antigen, George et al. nevertheless concludes "no competition was achieved", and the antibodies bind distinct, non-overlapping epitopes.

Therefore, the claims are *not* unambiguously interpreted, as it cannot be determined whether the antibody to which the claims are directed is an antibody that merely inhibits, but does not abrogate the interaction between the selected antibody and PSMA. Moreover, if the claimed antibody merely inhibits binding of the selected antibody to PSMA, it cannot be determined to what requisite extent the claimed antibody must "compete" for binding to PSMA with the selected antibody.

Applicant has argued because the monoclonal antibody to which independent claims 69, 124, 125, and 126 is selected from monoclonal antibodies that are produced by deposited hybridomas, the antibodies are defined with enough precision to permit one to determine whether they compete for binding to PSMA, but it is not apparent why Applicant has made such an assertion. The identity of the monoclonal antibody is necessarily known, otherwise one could not select an antibody capable of competing for binding to PSMA with the monoclonal antibody; but, regardless of the identity of the monoclonal antibody, as explained, it cannot be ascertained to what extent the antibody to which the claims are directed (i.e., the antibody administered to the subject) is an antibody that "competes" for binding to PSMA with the monoclonal antibody.

Moreover, it cannot be determined whether the antibody administered to the subject merely inhibits, or rather necessarily abrogates the interaction between PSMA and the selected monoclonal antibody.

Applicant has further argued that the Office's characterization of the disclosure of George et al., as illustrating the capricious and arbitrary nature of determinations that different antibodies bind to the same or different epitopes, which are based upon the results of competitive binding assays, such as the assay exemplified in the specification, is inaccurate. Applicant has contended to the contrary that the artisan is fully capable of determining whether or not an antibody "competes" for binding to an antigen with another antibody.

In reply, it is not contested that the artisan is capable of making a determination based upon the results of a competitive binding assay, such as the assay exemplified in the specification, that one antibody "competes" for binding with another; accordingly, the relevant point made in citing George et al. to support of the propriety of this ground of rejection is that the degree to which one antibody competes for binding to an antigen with another is expected to vary substantially, depending upon the binding specificities and affinities of the antibodies used in the assay, such that one might arbitrarily label the antibodies as either binding to "competing" or "non-competing" binding sites".

Notably Applicant has contended that the antibodies disclosed by George et al. do "compete", despite the opposite conclusion by George et al. that the antibodies do not. These remarks support the Office's position that the artisan cannot know the requisite degree to which the antibody administered to the subject must compete for binding to PSMA with the selected monoclonal antibody; and as such, the claims cannot be regarded as delineating the subject matter that is regarded as the invention with the necessary clarity and particularity to permit the skilled artisan to know or determine infringing subject matter.

Applicant has further remarked that, just as George et al. had presumably done, the practitioner of the claimed invention may carry out scientific experiments to determine a "reasonable threshold for competition", which identifies an antibody that is to be used in its practice. Moreover, Applicant has remarked that skilled artisans routinely carry out planned and controlled experiments to determine whether antibodies compete with one another, and they

would not arbitrarily add a concentration of an antibody so high as to give false positive results without testing other concentrations.

It is submitted that these remarks also support the Office's position that the claims are indefinite. The subject matter that is the claimed invention must be defined by the claims with clarity and particularity; the subject matter encompassed by the claims must not vary, but must instead by known or readily determinable. If, as Applicant's remarks might suggest, the practitioner of the claimed invention may carry out scientific experiments to determine a "reasonable threshold for competition", which presumably identifies an antibody that is to be used in its practice, the antibody to which the claims are directed is not limited to any clearly or particularly defined antibody; rather, the antibody might be any antibody that is somehow determined, perhaps arbitrarily so, to compete for binding to PSMA with the selected antibody, and thus the subject matter encompassed by the claims might vary significantly, depending upon just how high or low that "reasonable threshold for competition" is set.

It follows that if one cannot determine the requisite degree to which the antibody to be administered to the subject competes for binding to PSMA with the selected monoclonal antibody, because there is no known or disclosed standard for ascertaining this requisite degree, which may perhaps be similar, if not equivalent to Applicant's "reasonable threshold for competition", then how might the subject matter encompassed by the claim be known or determined? How might one reasonably conclude that the claims have delineated that subject matter, which is regarded as the invention, with the necessary clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph?

Finally, it is noted that Applicant has argued that a determination of whether or not an antibody competes for binding with another antibody was a well-established procedure at the time of filing.

The Examiner disagrees; while the methodology used to determine whether or not an antibody competes for binding to an antigen with another antibody may have been practiced routinely, the outcome, i.e., the conclusion reached by such experiments is not founded upon any well-established procedure or guideline, which unambiguously and consistently provides one with accurate, objective, and certain knowledge that the antibodies either compete for binding to the antigen or do not. Again, Applicant has contended that the antibodies disclosed by George et

al. do compete (Applicant's emphasis), despite the opposite conclusion by George et al. that the antibodies do not. So, while the methodological approach used by Applicant, as well as by George et al. to determine if an antibody competes for binding to an antigen with another antibody may have been routine at the time this application was filed, it is apparent that there was no consensus as to the requisite degree one antibody necessarily inhibits binding of the other before it is labeled a "competing" or a "non-competing" antibody (i.e., the value of the threshold level of inhibition that is observed in such assays, which defines the antibody as either a "competing" or a "non-competing" antibody, has not been established).

Therefore, without intending to acquiesce to Applicant's argument that a determination of whether or not an antibody competes for binding with another antibody was a well-established procedure at the time of filing, it is noted that Applicant has remarked that George et al. describes scientific experiments in which the "reasonable threshold for competition", i.e., 5-9% inhibition, indicated no competition. Might these remarks suggest that if any given antibody inhibits the binding of the selected antibody to a more significant extent (e.g., wherein at least 10% inhibition has been observed in a competition binding assay similar to that which has been disclosed in this application), the antibody is an antibody that is encompassed by the claims? Again, despite the routine nature of the methodology that might be used to determine if an antibody competes for binding to PSMA with the selected antibody, it would seem that Applicant's "reasonable threshold for competition" may vary substantially; however, it is improbable that the skilled artisan would provide a poorly competing antibody in practicing the claimed invention. A poorly competing antibody might not be reasonably expected to bind to the same epitope of PSMA as the selected monoclonal antibody; therefore for reasons discussed in greater detail below, a poorly competing antibody could not be predictably used to achieve the claimed objective of treating prostate cancer, unless it is conjugated to a cytotoxic moiety capable of inhibiting growth of prostate cancer cells. So, this raises the question, to what extent must the antibody administered to the subject be capable of competing for binding to PSMA with the selected antibody to be used effectively to treat prostate cancer, and how is Applicant's "reasonable threshold for competition" determined? The value of this threshold is not disclosed, so it stands to reason that it must be empirically determined. Were the claims given the broadest interpretation, the antibody that is administered to the subject might be any antibody that at least

partially inhibits binding of the selected monoclonal antibody to PSMA, but because the antibody must be suitable for use, if not effective in treating prostate cancer, even when not conjugated to a cytotoxic moiety capable of inhibiting the growth of prostate cancer cells, the claims might only be interpreted to encompass certain antibodies, which compete for binding to PSMA with the selected monoclonal antibody and are therapeutically effective. However, it is not apparent by what criteria the therapeutically effective antibody administered to the subject is selected, if not solely on the basis of the antibody's ability to compete for binding to PSMA with the selected monoclonal antibody. Therefore, absent a disclosure describing the value of the threshold of inhibition that defines the extent to which the antibody administered to the subject must compete, so as to be suitable for use, there are no means for establishing the metes and bounds of the subject matter that is encompassed by the claims and regarded by Applicant as the invention.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 69-74, 76-79, 124-127, 129, 130, 137-148, 150-168, 170-172, 186, and 190 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a method for treating prostate cancer in a subject, said method comprising administering to the subject an antibody or an antigen binding portion thereof that binds prostate specific membrane antigen (PSMA), wherein said antibody or antigen binding portion thereof is conjugated to a therapeutically effective cytotoxic agent, and wherein said antibody or antigen binding portion thereof binds to PSMA and competes for binding to PSMA with a monoclonal antibody selected from the group consisting of J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively, **or while being enabling for using** any other method for treating prostate cancer in a subject, *as taught by the prior art*, which falls within the scope of the present claims, **does not reasonably provide enablement for using** a method for treating prostate cancer in a subject, said method comprising administering to the subject any antibody or

an antigen binding portion thereof that competes for binding to PSMA with a monoclonal antibody selected from the group consisting of J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Beginning at page 19 of the amendment filed July 19, 2007, Applicant has traversed the propriety of maintaining this ground of objection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed

invention at the time the application was filed without undue and/or unreasonable experimentation.

(a) *The specification would not reasonably enable the skilled artisan to make the antibodies or antigen binding portions thereof to which the claims are directed without undue and/or unreasonable experimentation.*

The claims are directed to a genus of antibodies or antigen-binding fragments thereof, which do not necessarily bind to the same epitope as any of monoclonal antibodies J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109. Rather, because as evidenced by George et al. (cited *supra*), for example, an antibody need not bind the same epitope of an antigen to "compete" for binding to that antigen with another antibody, the claims should broadly, but reasonably be interpreted to encompass any antibody that binds to PSMA, and not necessarily an antibody that binds to the same epitope as any of monoclonal antibodies J591, J533, E99, and J415.

The claimed antibodies or antigen binding fragments thereof, which bind to PSMA and compete for binding to PSMA with any of the particularly recited monoclonal antibodies, include but are not limited to antibodies or antigen-binding fragments that bind to the same or a different epitope as a member of any of the recited pluralities of monoclonal antibodies; see, e.g., paragraph [0104] of the published application. As explained above, the specification describes monoclonal antibodies J591, J533, and E99 as each capable of interfering with binding of the others to PSMA but incapable of competing for binding to PSMA with monoclonal antibodies J415 and 7E11/CYT356, and vice versa. Because each of monoclonal antibodies J591, J533, and E99 interferes with the others, the specification teaches each binds to the same epitope of PSMA; and because none of monoclonal antibodies J591, J533, and E99 interfere with the binding of monoclonal antibodies J415 and 7E11/CYT356, and vice versa, the specification teaches the latter antibodies bind different epitopes.

Furthermore, the claims do not define the extent to which the claimed antibody or antigen binding fragment "competes", nor do they define the methodology by which such a determination is necessarily made, and under what conditions. As evidenced by George et al. (cited *supra*), for example, at a high enough concentration, or under certain conditions, *any*

antibody, but perhaps especially another antibody that binds the same antigen, or more particularly the same epitope recognized by another antibody or an overlapping epitope of the antigen, is expected to "compete" for binding to the antigen with the other antibody.

Applicant has argued that in selecting a suitable antibody, the skilled artisan would not simply saturate an assay system with such a high concentration of an antibody that it would be falsely determined that the antibody competes for binding to PSMA with the selected monoclonal antibody, and would instead carry out planned and controlled experiments of a routine nature to determine if the antibody competes. Thus, it is Applicant's position that it is a routine matter to determine if an antibody "competes" for binding to PSMA with the selected antibody, such that the antibody to be administered to the subject could be provided just as simply, and without undue and/or unreasonable experimentation.

In response to this argument, the point, here, is that the claims do not define the extent to which the claimed antibody or antigen binding fragment "competes", nor do they define the methodology by which such a determination is necessarily made, and under what conditions. Broadly but reasonably interpreted, the claims are directed to any antibody that at least partially inhibits the binding of one of the particularly recited monoclonal antibodies to PSMA, and which, considering the intended use of the invention, must be treat prostate cancer when administered to a subject under conditions effective to achieve this objective. It is however not evident what "threshold" level of inhibition defines the antibody that competes for binding to PSMA with any one of the monoclonal antibodies, which defines the antibody that is effective to treat prostate cancer; and as noted above, an antibody that poorly competes for binding to PSMA with the selected antibody is not reasonably expected to bind to the same epitope as the selected antibody and could therefore not be used in a predictable manner to achieve the claimed objective of the invention.

How is the antibody to which the claims are directed made and/or selected for use, if not solely upon the basis of the antibody's requisite ability to "compete"; and since there is no standard for ascertaining the requisite extent to which the antibody necessarily inhibits the binding of the selected monoclonal antibody to PSMA? It is submitted that contrary to Applicant's argument, the identification of a suitable and effective antibody would not be a simple, routine matter of carrying out some planned and controlled experiments to determine if

the antibody competes, but would actually involve a substantial amount of additional, relatively more complex investigative work designed to determine the necessary extent to which an antibody must compete, so as to be predictably effective to treat prostate cancer when administered to a subject under appropriate conditions to do so.

Furthermore, although the prior art enables one to make and use many antibodies, which under certain conditions, could demonstrably "compete" for binding to PSMA with any of monoclonal antibodies J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, many of such antibodies are not reasonably expected to function to inhibit the growth of prostate cancer cells, or to facilitate the effective treatment of prostate cancer.

It is again noted that Applicant has contended that the antibodies disclosed by George et al. do compete (Applicant's emphasis), despite the opposite conclusion by George et al. that the antibodies do not (page 16, paragraph 3, of the amendment of July 19, 2007). It is further noted that Applicant has remarked that George et al. describes scientific experiments in which the "reasonable threshold for competition", i.e., 5-9% inhibition, indicated no competition. Might these remarks suggest that if any given antibody inhibits the binding of the selected antibody to a more significant extent (e.g., wherein at least 10% inhibition has been observed in a competition binding assay similar to that which has been disclosed in this application), the antibody is an antibody that is encompassed by the claims?

Because a poorly competing antibody might not be reasonably expected to bind to the same epitope of PSMA as the selected monoclonal antibody, the poorly competing antibody could not be predictably used to achieve the claimed objective of treating prostate cancer, unless it is conjugated to a cytotoxic moiety capable of inhibiting growth of prostate cancer cells. As explained in greater detail below, antibodies that bind to different epitopes of an antigen often have entirely different effects upon the activities of the antigen or the cells to which they bind, despite their binding to the same antigen.

So, this raises the question, to what extent must the antibody administered to the subject be capable of competing for binding to PSMA with the selected antibody to be used effectively to treat prostate cancer, and how is requisite level of competition (i.e., Applicant's "reasonable threshold for competition") determined? Given the fact that the antibodies compete with one or

another monoclonal antibody, the value of this threshold is expected to vary, but nonetheless there is no disclosure of a standard for use in ascertaining its value.

Despite the routine nature of the methodology that might be used to determine if an antibody competes for binding to PSMA with the selected antibody, the determination of the requisite degree to which an antibody competes, which perhaps characterizes the antibody that is effective to treat prostate cancer, has not been established. This level must be determined empirically; and it is essential that one know the value of the requisite level of inhibition that must be observed in the competition binding assay, which defines the therapeutically effective antibody, since it would not be possible to select an antibody suitable for provision and administration otherwise.

Giving the broadest, reasonable interpretation of the claims, the antibody that is administered to the subject is any antibody that binds to PSMA, which at least partially inhibits binding of the selected monoclonal antibody to PSMA, but in light of the unpredictable effects of antibodies that bind different epitopes of an antigen, such as PSMA, the skilled artisan cannot know whether the antibody is therapeutically effective, if it is not conjugated to a cytotoxic moiety capable of inhibiting the growth of prostate cancer cells. So, because it is not apparent by what criteria the antibody administered to the subject is selected, if not solely on the basis of the antibody's ability to compete for binding to PSMA with the selected monoclonal antibody, it is submitted that the amount of guidance, direction and exemplification is neither reasonably commensurate in breadth with the claims nor reasonably enabling of the claimed invention. Moreover, absent a disclosure describing the value of the threshold of inhibition that defines the extent to which the antibody administered to the subject must compete, so as to be suitable for use, it appears that the specification provides no means for readily determining which antibody should be provided.

Applicant is again reminded that to satisfy the enablement requirement, reasonable correlation must exist between the scope of the claims and scope of enablement set forth in the specification. Although a specification need not, and preferably omits teachings well known in the prior art, in deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While

every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

It is submitted that the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify antibodies and antigen-binding fragments thereof that bind to PSMA, which under certain, albeit unspecified assay conditions "compete" for binding to PSMA with any member of the recited pluralities of monoclonal antibodies, and are effective to treat prostate cancer; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

(b) *The specification would not reasonably enable the skilled artisan to use the antibodies or antigen binding portions thereof to which the claims are directed to practice the claimed invention, so as to achieve the claimed objective, without undue and/or unreasonable experimentation.*

The claims are drawn to a method for treating prostate cancer in a subject, said method comprising administering to the subject an antibody or antigen-binding portion thereof, which binds to PSMA and competes for binding for binding to PSMA with monoclonal antibody E99, monoclonal antibody J415, monoclonal antibody J533, or monoclonal antibody J591.

As already note, inasmuch as the claims are directed to methods for treating prostate cancer, the antibody or antigen binding portion thereof to which the claims are directed *must be therapeutically effective*, otherwise the claimed invention cannot be practiced in a manner that achieves the claimed objective.

While the specification does not expressly define the outcome (or a measured endpoint that is representative thereof) of an effective treatment necessarily achieved by the claimed invention, at page 9, lines 28-35, it is noted the specification describes the invention as "a method of ablating or killing normal, benign hyperplastic, and cancerous prostate epithelial cells". Accordingly, it is apparent the outcome of an effective treatment may comprise, for example, the killing of cancerous prostate cells. Additionally, as the specification describes the

biological agent, which is administered to the subject upon practicing the claimed invention, as either used alone or is bound to a substance effective to kill prostate cancer cells upon its binding to the cells (page 9, lines 33-35), it is apparent that the antibody or antigen binding portion thereof must be therapeutically effective *alone* to kill prostate cancer cells (i.e., in the absence of an attached therapeutic moiety), or otherwise therapeutically effective when bound to a therapeutic moiety.

Notably, the prior art teaches effective treatment of prostate cancer using antibodies that bind the extracellular domain of PSMA, albeit not necessarily antibodies that compete for binding to PSMA with monoclonal antibody E99, monoclonal antibody J415, monoclonal antibody J533, or monoclonal antibody J591, but only *where the antibody is conjugated or covalently linked to a cytotoxic substance*, such as a therapeutic drug or radioisotope.

Claims 124-127, 136-138 (in part), 139-152, 154 (in part), 155, 156-163 (in part), 164-173, 186, and 190 (in part) are directed to members of the genus of antibodies or antigen-binding portions thereof, which comprise a cytotoxic drug (e.g., a therapeutic drug or a compound emitting radiation).

Claims 157 and 158 are directed, at least in part, to members of the genus of antibodies or antigen binding portions thereof, which, are not necessarily conjugated to cytotoxic drug, but are effective to initiate complement-mediated cellular cytotoxicity (CMCC) or antibody-dependent cellular cytotoxicity (ADCC) against the prostate cancer cells expressing PSMA to which they bind and are therefore therapeutically effective to kill prostate cancer cells by one or the other mechanism.

Otherwise, however, the claims encompass methods for treating prostate cancer in a subject, which comprise administering to the subject a *naked* antibody (i.e., an antibody that is *not* conjugated to a cytotoxic agent or prodrug) that need not mediate ADCC or CMCC against PSMA expressing prostate cancer cells, which competes for binding to PSMA with monoclonal antibody E99, monoclonal antibody J415, monoclonal antibody J533, or monoclonal antibody J591, so as to be therapeutically effective, in and of itself, upon its administration to a subject afflicted by prostate cancer.

As will be shown, the prior art teaches that the skilled artisan cannot predict whether a naked antibody or antigen binding portion thereof, which is *not* conjugated to a cytotoxic moiety,

is effective to kill the cells to which it binds, unless it is known that the antibody mediates ADCC or CMCC against those cells.

The specification fails to remedy the deficiency of the prior art to enable the skilled artisan to practice the claimed invention without undue and/or unreasonable experimentation, as it does not particularly describe any one antibody or antigen binding portion thereof that competes for binding to PSMA with monoclonal antibody E99, monoclonal antibody J415, monoclonal antibody J533, or monoclonal antibody J591 that is not conjugated to a therapeutically effective cytotoxic drug, and does not mediate either ADCC or CMCC, which is used to practice the claimed invention.

Moreover, as noted in the preceding Office action, it is submitted that Henry et al. (*Cancer Res.* 2004 Nov 1; **64**: 7995-8001) (of record) provides factual evidence that *naked* antibodies that bind the extracellular domain of PSMA, as expressed by prostate cancer cells, which are not conjugated to a cytotoxic agent, have no antitumor activity. More particularly, as previously explained Henry et al. teaches an unconjugated anti-PSMA antibody had no effect upon the growth of the cancer cells, whereas an immunoconjugate comprising this antibody and the drug maytansinoid 1 (DM1) was effective to suppress the growth of prostate cancer in a subject; see entire document (e.g., the abstract; and page 7998, Figure 3A). Moreover, Henry et al. reports the effect of the *naked* antibody upon the growth of the tumor cells in the subject was not significantly different from the effect of the vehicle control (i.e., the buffer, PBS, which was used as a carrier); see, e.g., page 7997, column 1.

Applicant has argued that the disclosure of Henry et al. is irrelevant, but the Examiner disagrees.

As explained in the preceding Office action, while perhaps the antibody described by Henry et al. (cited *supra*) does not bind to the same epitope of the extracellular domain of PSMA as any of the monoclonal antibodies E99, J415, J533, and J591, which are described in the instant application, and may not be effective to substantially compete for binding to PSMA with these antibodies, there is no factual evidence of record that suggests the lack of effect by the naked antibody of Henry et al. is explained by its binding to a different epitope of PSMA.

Even so, McDevitt et al. (*Cancer Res.* 2000 Nov 1; **60**: 6095-6100) (of record) reports an alpha-particle emitting radioimmunoconjugate comprising monoclonal antibody J591 (i.e., one

of the four monoclonal antibodies to which the instant claims is specifically directed) effectively stopped the growth of LNCaP prostate cancer cells *in vitro*, but the unlabeled monoclonal antibody produced no substantial effect; see entire document (e.g., the abstract; and page 6098, Figure 4).

Applicant has argued that the disclosure of McDevitt et al. is not relevant; but the Examiner disagrees.

McDevitt et al. shows that even were an antibody to bind to the *same* epitope as any of monoclonal antibodies E99, J415, J533, and J591, the skilled artisan cannot predict whether that antibody, when not conjugated to a cytotoxic agent, is used effectively to kill the cells to which it binds.

It is for this reason that it has been submitted that the disclosure would not have reasonably enabled the skilled artisan to practice the claimed invention, as of the filing date sought by Applicant, without undue and/or unreasonable experimentation, as the therapeutic effectiveness of the antibody or antigen binding portion thereof, if not conjugated to a cytotoxic drug or prodrug, or not known to mediate ADCC or CCMC, must be determined empirically.

Then, with particular regard to claims 157 and 158, Morris et al. (*Clin. Cancer Res.* 2005 Oct 15; **11** (2): 7454-7461) (of record) discloses, prior to October 2005, the *in vivo* activity of unlabeled, naked humanized antibody J591 (again, i.e., one of the four monoclonal antibodies to which the instant claims is specifically directed), and particularly its ability to activate therapeutically effective ADCC in treated subjects, had *not been explored*; see entire document (e.g., the abstract).

Although Morris et al. reports, "increasing doses of antibody are associated with higher rates of patients with ADCC reactivity [...] and higher median percent LNCaP cell lysis" (page 7458, column 2), Morris et al. also reports only one of 14 patients had any measurable objective response, as determined by measurement of the surrogate endpoint, namely a PSA decline[2], whereas 11 patients progressed, one had a marginal response, and one showed stable disease (page 7459, column 1). Moreover, Morris et al. teaches the antibody is ineffective to mediate

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[2] The patients were treated with radiolabeled, or a combinantion of radiolabeled and unlabeled deimmunized monoclonal antibody J591 (page 7455, paragraph bridging columns); and Morris et al. does

CMCC, as it does not bind complement and therefore not surprisingly induced no significant change in C3 and C4 levels in the treated subjects (page 7458, column 2).

Applicant has argued that the Office has misinterpreted the data presented by Morris et al., and that the study described by Morris et al. was a pilot trial with an unlabeled antibody, designed to explore the effects of dose escalation on pharmacokinetics, biodistribution and ADCC activation, which does not support the Office's position that the claimed invention could not be practiced without undue and/or unreasonable experimentation. Moreover, Applicant has argued that Morris et al. demonstrates that an unconjugated anti-PSMA antibody is therapeutically effective because Morris et al. discloses that PSA levels in a treated patient declined after treatment, whereas three treated patients were found to have stabilized levels of PSA (one of which has stabilized disease).

In response, contrary to Applicant's assertions the patients were not treated with unconjugated antibody. Rather, as explained in the preceding Office action, the patients were treated with a radiolabeled deimmunized monoclonal antibody J591, or they were treated with a combination of a radiolabeled and an unlabeled antibody (page 7455, paragraph bridging columns).

Furthermore, as also previously explained and again noted above, Morris et al. reports only one of 14 patients had any measurable objective response, i.e., a PSA decline, whereas 11 patients progressed, one had a marginal response, and one showed stable disease (page 7459, column 1). Pilot study or not, it is submitted that the disclosure by Morris et al. indicates that the claimed invention could not be used to achieve the claimed effect without undue and/or unreasonable experimentation because, for one, the study does not establish the therapeutic effectiveness of a naked anti-PSMA antibody, and this deficiency has not been remedied by Applicant's disclosure, which similarly fails to describe with any of the requisite particularity necessary an antibody that binds to PSMA and competes for binding to PSMA with a monoclonal antibody selected from monoclonal antibodies E99, J415, J533, and J591, which is effective to treat prostate cancer, when *not* conjugated to a cytotoxic moiety.

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not indicate whether the growth inhibitory effects of the treatment were mediated by the resultant irradiation of the targeted prostate cancer cells, by ADCC, or both.

Again, as previously explained, while there is an assertion in the specification that any of monoclonal antibodies E99, J415, J533, and J591 may be effective to mediate ADCC or CCMC, it discloses no data or scientifically based reasoning to support the assertion[3]. Accordingly, in view of Morris et al. (cited *supra*), it would seem as of the filing date sought by Applicant the claimed invention could not have been practiced, even using the particularly described monoclonal antibody J591, without undue and/or unreasonable experimentation, as it would have first been necessary to empirically determine whether the antibody or portion thereof effectively mediates ADCC or CMCC[4], and then whether it is used effectively to treat prostate cancer in a subject.

Applicant has further remarked that Morris et al. discloses that the deimmunized version of monoclonal antibody J591, which was administered to the patients, caused 50% of the patients to show ADCC activation[5].

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[3] The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). The prior art shows the skilled artisan cannot predict whether any given antibody or portion thereof, which binds to PSMA, is capable of mediating ADCC or CMCC.

"[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that describes with particularity any one member of the genus of antibodies or portions thereof that bind PSMA-expressing prostate cancer cells to mediate ADCC or CMCC against those cells. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

"Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004). Without the antibodies to which the claims are directed, it is impossible to use the claimed invention.

[4] Kim et al. (*Int. J. Cancer.* 2002; **102**: 428-434) teaches the skilled artisan cannot predict whether an antibody or portion thereof is capable of mediating ADCC, since it ability to do so depends upon both the isotype of the antibody and the epitope of the antigen to which it binds; see entire document (e.g., the abstract).

In addition, Kinoshita et al. (*Prost. Cancer Prost. Dis.* 2005; **8**: 359-363) teaches the need to identify the epitopes of PSMA to which antibodies capable of mediating ADCC bind; see entire document (e.g., page 359, column 2).

[5] Morris et al. discloses: "As can be seen in the table [i.e., Table 5], increasing doses of antibody are associated with higher rates of patients with ADCC reactivity (>15% LNCaP cell lysis) and higher median percent LNCaP cell lysis. All pretreatment sera showed 5% LNCaP cell lysis."

In response, inasmuch as the claims are directed to a method for treating prostate cancer, it is important to note that Morris et al. does not indicate whether the growth inhibitory effects of the treatment were mediated by the resultant irradiation of the targeted prostate cancer cells, by ADCC, or both[6].

In addition, only a few claims are directed to monoclonal antibody J591, or an antibody that competes for binding to PSMA with monoclonal antibody J591, as opposed to one of the other monoclonal antibodies. Yet, as explained in the preceding Office action, Kim et al. (*Int. J. Cancer.* 2002; **102**: 428-434) (of record) teaches the skilled artisan cannot predict whether an antibody or portion thereof is capable of mediating ADCC, since it ability to do so depends upon both the isotype of the antibody and the epitope of the antigen to which it binds; see entire document (e.g., the abstract). The antibody to which the claims are directed need not be of the same isotype as the deimmunized version of the monoclonal antibody J591, which was administered to the patients showing ADCC activation following treatment. Then, Kinoshita et al. (*Prost. Cancer Prost. Dis.* 2005; **8**: 359-363) (of record) teaches the need to identify the epitopes of PSMA to which antibodies capable of mediating ADCC bind; see entire document (e.g., page 359, column 2). As explained, though an antibody may compete with monoclonal antibody J591 for binding to PSMA, it does not necessarily bind to the same epitope of PSMA as the monoclonal antibody.

Furthermore, only claim 158 is directed to an antibody that is effective to initiate an endogenous host immune function, wherein said function is ADCC; claim 157 is directed to an antibody that is effective to initiate CMCC. Again, Morris et al. teaches the antibody is ineffective to mediate CMCC, as it does not bind complement and therefore not surprisingly induced no significant change in C3 and C4 levels in the treated subjects (page 7458, column 2).

Because only one patient engaged a sustained PSA decline of 90%, Applicant has remarked that Morris et al. has suggested it is possible that the optimal patient population for studying the effects of an unlabeled antibody was not chosen.

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[6] ADCC activation was measured *in vitro* using isolated specimens acquired from different patients given different doses of the antibody at different time points; see, e.g., page 7459, Table 5; and page 7456, column 1.

While Morris et al. is a post-filing date publication, and so could not be relied upon anyway to remedy the deficiencies of the disclosure to reasonably enable the skilled artisan to use the claimed invention to achieve the claimed therapeutic effect[7], these remarks tend to support the Office's position. If the optimal patient population for studying the effects of an unlabeled antibody was not chosen, it follows that the results of that study should not be relied upon to determine those effects.

Applicant has remarked that the remaining references cited by the Office do not undermine the evidence provided by Morris et al.

In response to this remark, it is the disclosure of the instant application that must reasonably enable the skilled artisan to use the claimed invention to achieve the claimed therapeutic effect; and, as noted above, it is improper to rely upon post-filing date publications, such as Morris et al. to correct the deficiencies of that disclosure. Nevertheless, it is aptly noted that Morris et al. does not provide factual evidence that the claimed invention can be used to achieve the claimed therapeutic effect; moreover, the evidence provided by Morris et al. is not reasonably commensurate in scope with the breadth of the claims, which are not limited to a method for treating prostate cancer by administering to the patient a deimmunized version of the monoclonal antibody J591.

Applicant has further remarked that Henry et al. discloses that the antibody moiety of the immunoconjugate may engage immune responses that would contribute to efficacy in patients, but that possibility which cannot be determined using the immunocompromised mouse models that were used.

Perhaps so, but that is precisely the point: Henry et al. disclosed that the antibody moiety **may** engage immune responses that could increase the efficacy of the treatment, but that one could not extrapolate their findings to even guess the outcome of such a treatment to engage immune responses in humans. Henry et al. reports the effect of the *naked* antibody upon the growth of the tumor cells in the subject was not significantly different from the effect of the vehicle control (i.e., the buffer, PBS, which was used as a carrier); see, e.g., page 7997, column

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[7] Supporting documents cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks. See MPEP § 2164.05(a).

1. Because the mice were immunocompromised, however, even if the antibody were capable of stimulating an immune function (e.g., ADCC or CCMC), one could not know that to be the case.

Then, Applicant has argued that because McDevitt et al. discloses a study in which athymic, immunocompromised mice were used to assess the effectiveness of a radiolabled anti-PSMA antibody to inhibit the growth of xenografted LNCaP prostate cancer cells, one could not conclude that the observed lack of effect by the unlabeled antibody provides an indication that it would not be effective in humans.

In reply, the Office has made no such conclusion. The prior Office action only addresses the point that while McDevitt et al. reports an alpha-particle emitting radioimmunoconjugate comprising monoclonal antibody J591 effectively stopped the growth of LNCaP prostate cancer cells *in vitro*, the unlabeled monoclonal antibody produced no substantial effect. If so, this study indicates that the *naked* antibody, which is not conjugated to a cytotoxic moiety (e.g., a radioisotope), lacks an inhibitory effect, in and of itself. Accordingly, as explained previously, if the antibody is not conjugated to a cytotoxic moiety, and it lacks the ability to mediate ADCC, CMCC, or both, it is not reasonably expected to achieve the claimed therapeutic effect when administered to a patient afflicted by prostate cancer. Morris et al. teaches a deimmunized version of monoclonal antibody J591 lacks the ability to mediate CMCC; and while it appears capable of mediating ADCC, only one of 14 patients had any measurable objective response, as determined by measurement of the surrogate endpoint, namely a PSA decline, whereas 11 patients progressed, one had a marginal response, and one showed stable disease, so there remains a possibility, as Morris et al. explains, that the patient population chosen for an assessment of the effects of the naked, unconjugated antibody was inappropriate.

Again, claims 124-127, 136-138 (in part), 139-152, 154 (in part), 155, 156-163 (in part), 164-173, 186, and 190 (in part) are directed to members of the genus of antibodies or antigen-binding portions thereof, which comprise a cytotoxic drug (e.g., a therapeutic drug or a compound emitting radiation); and only claims 158 is specifically directed to members of the genus of antibodies or antigen binding portions thereof, which though not necessarily conjugated to cytotoxic drug, are nevertheless effective to initiate ADCC against the prostate cancer cells expressing PSMA to which they bind.

With regard to the other references cited (e.g., Stancovski et al.), Applicant has argued that the disclosures are irrelevant.

The Examiner disagrees because the citation of each these other references helps to establish the state of the art, now or at the time the application was filed; furthermore, their disclosures indicate the level of skill in the art, which although high, is hindered by an evident high degree of unpredictability. Moreover, as discussed previously, the prior art teaches the skilled artisan cannot predict the effect of an antibody upon the growth of cancer cells, since it is well understood that antibodies binding the same antigen, or even the same epitope of an antigen, may have strikingly different effects.

Stancoviski et al. *(Proceedings of the National Academy of Science USA.* 1991; **88**: 8691-8695) (of record), for example, characterized the binding effects upon the growth of tumor cells of different antibodies, each of which bind different epitopes of the extracellular domain of a tumor-associated antigen related to EGFR, namely ErbB2; see entire document (e.g., the abstract). Stancovski et al. teaches some anti-ErbB2 antibodies inhibited tumor cell growth, but others actually *accelerated* their growth (page 8693, column 1).

Xu et al. (*Int. J. Cancer.* 1993; **53**: 401-408) (of record) has characterized similarly differential effects of another panel of antibodies that bind the same antigen, albeit different epitopes; see entire document (e.g., the abstract).

Then, by way of explanation, Jiang et al. (*J. Biol. Chem.* 2005 Feb 11; **280** (6): 4656-4662) (of record) teaches that it is well known that different biological effects are associated with epitope specificity of the antibodies; see entire document, particularly page 4656, column 2.

In addition, De Santes et al. (*Cancer Res.* 1992 Apr 1; **52**: 1916-1923) (of record) teaches administering radiolabeled anti-ErbB2 (Her-2/*neu*) monoclonal antibody 4D5 to a subject caused a marked inhibition of tumor growth in the subject; however, the unlabeled, naked antibody had no effect on tumor progression; see entire document (e.g., the abstract; page 1921, Figure 7).

Therefore, again, unless the antibody or antigen binding portion thereof is conjugated to a cytotoxic drug, the prior art teaches it cannot be know or determined whether an antibody is capable of inhibiting the growth of cancer cells, or more particularly, whether it is used effectively to treat prostate cancer. Thus, given such evident unpredictability, the prior art teaches the effectiveness of an antibody is necessarily determined empirically, and consequently,

as of the filing date sought by Applicant, the skilled artisan could not have used the claimed invention without undue and/or unreasonable experimentation.

It follows from the above discussion of the related prior art that the mere generalized description of antibodies, as binding a well-characterized tumor-associated antigen, as opposed to a well-characterized epitope of an antigen, cannot always suffice to adequately describe the antibodies to which the claims are directed, namely antibodies that have an inhibitory and therapeutic effect, because the skilled artisan could not distinguish those antibodies that bind an antigen on tumor cells and inhibit the growth of those tumor cells from antibodies that bind the antigen but lack therapeutic effect (e.g., promote the growth of tumor cells) without undue and/or unreasonable experimentation.

In further support of this position, the prior Office action additionally cites Boyer et al. (*Int. J. Cancer.* 1999; **82**: 525-531) (of record). Boyer et al. teaches different epitopes of a tumor-associated antigen (i.e., Her-2) can serve as distinct targets for immunotoxins; see entire document (e.g., the abstract). Boyer et al. teaches a panel of antibodies conjugated to a cytotoxic moiety, which bind to discrete epitopes, produced markedly different cytotoxic effects that did not correlate with the isotype of the antibody, its binding affinity, the relative position of its epitope, or its internalization by the targeted cells; see, e.g., the abstract. Similar epitopic-dependency has been described by Press et al. (*J. Immunol.* 1988 Dec 15; **141** (12): 4410-4417) (of record); ricin A-chain comprising immunotoxins directed against different epitopes of an antigen differ markedly in their ability to kill the targeted cells (see entire document, e.g., the abstract).

Indeed, Riemer et al. (*Mol. Immunol.* 2005; 42: 1121-1124) (of record) teaches, because antibodies binding the same antigens have been shown to both ameliorate and aggravate disease symptoms, the concept of epitope specificity, as opposed to mere antigen specificity, in humoral immunology has gained importance in modern medicine the diverse biological effects; see entire document, particularly page 1123, column 1.

The epitope of PSMA to which monoclonal antibodies E99, J415, J533, and J591 bind has not been characterized, so it is not plausible that the skilled artisan can select an antibody that

binds to the same epitope as any one of these antibodies without undue and/or unreasonable experimentation[8].

Were the antibody to which the claims are directed to bind an overlapping, as opposed to the same epitope, the prior art teaches the skilled artisan cannot predict whether the antibody, even when conjugated to a cytotoxic moiety, is used effectively to treat prostate cancer. For example, Pettersen et al. (*J. Immunol.* 1999 Jun 15; **162** (12): 7031-7040) (of record) teaches anti-hIAP (CD47) monoclonal antibodies Ad22 and 1F7, which induce apoptosis of Jurkat T cells and peripheral blood mononuclear cells (PBMC) expressing the antigen to which these antibodies bind; but Pettersen et al. also teaches other antibodies, namely monoclonal antibodies 2D3 and B6H12 that commonly bind to hIAP/CD47, which *do not induce apoptosis* of the cells to which it binds; see entire document (e.g., the abstract; and page 7033, column 1). As might be expected, given the recognized epitope-dependency of the various effects caused by different antibodies binding the same antigen, Pettersen et al. teaches monoclonal antibody 2D3 and Ad22 bind discrete epitopes; but curiously Pettersen et al. teaches monoclonal antibody B6H12, despite its apparent inability to induce apoptosis, binds an epitope that overlaps the epitopes to which monoclonal antibodies Ad22 and 1F7 (see, e.g., page 7032, column 2). Similarly, Bernard et al. (*Human Immunol.* 1986; **17**: 388-405) (of record) describes differential effects by antibodies binding "competing" antigenic sites or epitopes. Thus, the prior art suggests that a description of a genus of antibodies as competing for binding of another antibody known to cause a desired

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[8] The term "epitope", as it is used in the art of immunology, is more generally used in a broader context to mean an "antigenic determinant", or site on the surface of an antigen molecule to which a single immunoglobulin molecule (e.g., antibody) binds; generally an antigen has several or many different antigenic determinants and reacts with antibodies of many different specificities. Stedman's Online Medical Dictionary, 27th Edition, which is available on the Internet at http://www.stedmans.com/, for example, defines the term "epitope' as "[t]he simplest form of an antigenic determinant, on a complex antigenic molecule, which can combine with antibody or T cell receptor".

Again, Greenspan et al. (cited *supra*), for example, teaches that defining epitopes is not as easy as it seems; and given this fact, it follows the epitope to which any given ligand binds can only be identified empirically.

Thus, as explained above, even using a competition binding assay, such as that described in Example 10 of the specification, the skilled artisan cannot recognize or distinguish an antibody that binds the same epitope as another antibody because antibodies that compete with one another for binding to the same antigen do not necessarily bind the same epitope; rather, an antibody may bind a spatially overlapping epitope and thereby sterically hinder binding of the other ligand to its epitope, or as evidenced by George et al. (discussed in further detail below), an antibody may bind an epitope that is distant from, and spatially non-overlapping with the epitope of an antigen recognized by the other antibody, and still interfere with binding of the latter to the antigen.

effect may not be sufficient to describe the genus of antibodies having that same effect; and as such, it is submitted the claimed invention could not be practiced, as of the filing date sought by Applicant, without undue and/or unreasonable experimentation, as it would be necessary to empirically determine whether or not an antibody or portion thereof is used effectively to treat prostate cancer.

Now, having made that point, despite any assertion otherwise, it is aptly noted that claims are not necessarily directed to antibodies or antigen binding fragments thereof that bind to the same epitope of PSMA as any of monoclonal antibodies E99, J415, J533, and J591, but rather to any antibody capable of competing for binding with one of these four monoclonal antibodies to PSMA.

The specification alleges that an antibody that competes for binding to PSMA with an E99, a J415, a J533, and a J591 monoclonal antibody necessarily binds the same antigenic determinant or epitope; see, e.g., page 37, line 24, through page 39, line 16. This is not necessarily true, as will be explained; and it is aptly noted that the term "competes" is not expressly defined in the specification, so it is not immediately determinable, given the instant disclosure, what functional attribute characterizes the antibody or antigen binding fragment thereof, which is used effectively in practicing the claimed invention; moreover, it is further noted, as discussed in greater detail below, the requisite degree to which the antibody "competes" for binding to PSMA with any one of the recited monoclonal antibodies, nor the methodology used to make such a determination, and the conditions under which that determination are made, are ascertainable from the disclosure. As such, it is submitted the amount of guidance, direction, and exemplification set forth by the disclosure is not reasonable commensurate in scope with the breadth of the claims, would not permit the skilled artisan to immediately identify antibodies that are suitable, and would not therefore reasonably enable the practice of the claimed invention without undue and/or unreasonable experimentation.

As noted above, the term "competition" is defined, for example, by Stedman's Online Medical Dictionary, 27th Edition as meaning: "The process by which the activity or presence of one substance interferes with, or suppresses, the activity of another substance with similar affinities" (Copyright © 2006 Lippincott Williams & Wilkins). Given this definition, the claims are directed to antibodies or antigen-binding fragments thereof that interfere with, or suppress

binding of one of the selected monoclonal antibodies to PSMA, as perhaps determined using the exemplified binding assay.

Again, this interpretation is not inconsistent with the specification, which at paragraph [0106], for example, discloses: "The results indicated that J591, J533, and E99 each **interfere, compete, or block** binding of one another but do not block binding of J415 and vice versa" (emboldened for emphasis).

Thus, while one may know how to determine whether an antibody "competes" with one of the selected monoclonal antibodies, it is apparent that the degree to which an antibody competes with another antibody is a relative or subjective expression, and the requisite degree to which the claimed antibody competes with any of the selected monoclonal antibodies cannot be ascertained from the disclosure.

Contrary to the assertion in the specification that such a binding assay determines whether two antibodies bind to the same antigenic determinant (i.e., epitope), competing antibodies do not necessarily bind the same epitopes. For example, "competing" antibodies may bind spatially overlapping but discrete epitopes. Simply because two antibodies cannot simultaneously occupy the same space, such an antibody, once bound to the antigen, sterically hinders or blocks binding of another such antibody. As another example, a "competing" antibody might not necessarily bind to the same epitope of an antigen as another antibody, if one of the antibodies induces conformational shifts in the three-dimensional structure of the antigen upon binding, which prevents binding of the other antibody to the antigen because the epitope to which it would otherwise bind is unrecognizable as a consequence of the structural change.

In addition, it is recognized that the degree of binding of an antibody, which is observed in the exemplified competitive binding assay, will depend upon the concentration of the detectably labeled antibody and the unlabeled competing antibody. Typically, the higher the concentration of the unlabeled competitor, the lower the percentage of binding of the labeled antibody. So, at *high enough* concentrations, any antibody might be deemed capable of "competing" for binding to an antigen with any other antibody, regardless of whether or not the different antibodies bind to the same, or even overlapping epitopes.

As explained above, George et al. (cited *supra*), for example, describes different antibodies, which do not bind to the same epitope of an antigen, but are nevertheless capable of

competing with one another for binding to the antigen; see entire document (e.g., page 903, paragraph bridging columns 1 and 2). Furthermore, as also explained above, George et al. illustrates the capricious and arbitrary nature of determinations that different antibodies bind to the same or different epitopes, which are based upon the results of competitive binding assays, such as the assay exemplified in the specification. Again, although each of the described antibodies "competed" to a measurable extent with the other antibodies for binding to the antigen, George et al. nevertheless concludes "no competition was achieved", and the antibodies bind distinct, non-overlapping epitopes.

It cannot be determined whether the antibody to which the claims are directed is an antibody that merely inhibits, but does not abrogate the interaction between the selected antibody and PSMA. If the claimed antibody merely inhibits binding of the selected antibody to PSMA, it cannot be determined to what requisite extent the claimed antibody must "compete" for binding to PSMA with the selected antibody.

Although the prior art enables one to make and use many antibodies, which under certain conditions, could demonstrably "compete" for binding to PSMA with any of monoclonal antibodies J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, and while the skilled artisan could potentially screen such "competing" antibodies to identify those that are therapeutically effective to treat prostate cancer, Applicant is reminded that to satisfy the enablement requirement, reasonable correlation must exist between the scope of the claims and scope of enablement set forth in the specification. Furthermore, although a specification need not, and preferably omits teachings well known in the prior art, in deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify antibodies and antigen-binding fragments thereof, which under certain, albeit unspecified assay conditions "compete" for binding to PSMA with any one of the recited monoclonal antibodies; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

Finally, with regard to claim 190, which is directed to method according to claim 69, 124, 125, 126, or 127, which is effective to prevent or delay the progression of prostate cancer in the subject, the amount of guidance, direction and exemplification would not reasonably enable the skilled artisan to use the claimed invention without undue and/or unreasonable experimentation. If the antibody or antigen binding portion thereof were administered to a subject prior to the onset of the disease, so as to prevent its occurrence and progression, it is submitted the specification fails to provide the guidance and direction necessary to select patients in whom the invention is used effectively, and moreover, as PSMA is expressed by normal prostatic epithelial cells, as well as other normal tissue, it would seem likely that the cost of such treatment would outweigh the benefit, as the treatment would undesirably affect the growth and/or survival of normal cells. Furthermore, there is no factual evidence of record that supports the assertion that the disease is preventable, regardless of whether or not the patient is treated using the claimed invention. Similarly, there is no factual evidence of record that supports the assertion that the claimed method is effective to prevent the progression of the disease, as Morris et al. (cited *supra*), for example, teaches to the contrary monoclonal antibody J591 was not effective to prevent disease progression (page 7459, column 1).

Applicant has argued that the amendment to claim 190 makes clear that the invention is not a method for preventing prostate cancer. Applicant has further argued that the claim is directed to a process that prevents the progression of prostate cancer.

In response, why would one limit the claimed subject matter to a process for treating prostate cancer in accordance with any of claims 69, 124, 125, 126, and 127, wherein the method prevents the progression of an established tumor? Might not the prevention of the progression of prostate cancer be more liberally read to include the prevention of prostate cancer in the patient, even before it has established? Tumorigenesis is a process with a beginning that is not so easily defined as the tumor ultimately produced by that process. Nonetheless, tumorigenesis *progresses* from this poorly defined starting point; so, the claim should be more broadly read as encompassing a method for preventing prostate cancer from its outset. This broad interpretation is not inconsistent in light of the original claims and the disclosure describing the invention.

Applicant has argued that the publication of Morris et al. should be regarded as unequivocal evidence showing that the claimed invention can be used to prevent the progression

of an established tumor, given their disclosure that one patient in the study showed a PSA decline and three others showed PSA stabilization.

In response, again, Applicant is reminded that Morris et al. cannot be relied upon to remedy the deficiencies of the instant specification to reasonably enable the use of the claimed invention.

Furthermore, Applicant is also reminded that the showing by Morris et al. is not reasonably commensurate in breadth with that of the claims.

Finally, as explained, PSA levels are but one indication of response measured in the disclosed study of Morris et al.; the assessment also involved analyses of the lesions by bone scan and soft tissue imaging. At page 7456, column 2, Morris et al. discloses the following:

> Per WHO criteria, patients with measurable disease were categorized as having had (a) complete response if all measurable lesions disappeared; (b) partial response if they showed a ~50% reduction in the sum of the products of the longest perpendicular diameters of measurable lesions in the absence of new lesions; (c) stable disease if they did not meet either of the above two criteria; or (d) progressive disease if they showed a >25% increase in the sum of the products of the longest perpendicular diameters of the measurable lesions, or the appearance of new lesions. When the response decision was based on post-therapy PSA changes, the outcomes were normalization, decrease, or stabilization in PSA.

Morris et al. reports only one of 14 patients had an objective response; this patient was treated with a combination of a labeled antibody and an unlabeled antibody, and subsequently demonstrated a PSA decline (page 7459, column 1). The patient's bone scan and soft tissue imaging revealed stable disease. However, the patient's PSA levels increased following the last dose of antibody, albeit without reaching pretreatment levels before his withdrawal from the study. Eleven of 14 patients progressed, despite treatment; one had a "marginal" response, and one showed stable disease. Thus, none of the patients had a complete response (i.e., all measurable lesions disappeared), and it is questionable as to whether or not any of the patients has a partial response (i.e., showed a ~50% reduction in the sum of the products of the longest perpendicular diameters of measurable lesions in the absence of new lesions).

It is submitted that contrary to Applicant's opinion, the artisan might not reasonably regard Morris et al. as *unequivocal* evidence that the claimed invention can be used to treat prostate cancer, or more particularly prevent or delay the progression of the disease. The claims are directed to a method for treating prostate cancer, which includes, but is not limited to a

method that is effective to delay its progression. While the disclosure by Morris et al. would suggest that a radiolabeled deimmunized version of the monoclonal antibody of J5591 may in fact be used to effectively delay the progression of an established tumor, it fails to provide a showing that any antibody that binds to PSMA and competes for binding with PSMA with any of monoclonal antibodies J591, J533, E99, and J415 is effective to treat prostate cancer.

Accordingly, while Applicant's arguments traversing the propriety of maintaining this ground of rejection have been carefully considered, there appears to be a preponderance of factual evidence, now of record, indicating the skilled artisan could not practice the claimed invention to effectively treat prostate cancer in a subject without undue and/or unreasonable experimentation. Among the reasons, it does not appear that the disclosure would not reasonably enable one to make, identify, and/or select an antibody that is used effectively to do so.

Therefore, in conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. The rejection of claims 69-71, 77-80, 125, 126, 129, 130, 136-140, 144, 150, 152-154, 156-161, 164, 165, 171-173, 186, and 190 under 35 U.S.C. 102(e), as being anticipated by U.S. Patent No. 6,962,981 B1, as evidenced by Liu et al. (*Cancer Res.* 1998 Sep 15; **58**: 4055-4060) (of record; cited by Applicant) and George et al. (*Circulation.* 1998; **97**: 900-906) (of record), is maintained.

At page 28 of the amendment filed July 19, 2007, Applicant has traversed the propriety of this ground of rejection, arguing that the declaration under 37 C.F.R. § 1.131 by Neil H. Bander provides evidence of conception and reduction to practice by Applicant of the claimed invention in the United States prior to March 25, 1996, such that U.S. Patent No. 6,962,981 B1 is not prior art.

Applicant's argument has been carefully considered but not found persuasive for the following reasons:

The merit of the declaration by Dr. Bander has been carefully considered but not found sufficient to antedate the applied reference.

37 C.F.R. § 1.131(b) states:

> The showing of facts shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application.

The declaration by Dr. Bander provides evidence that Applicant had possession of the monoclonal antibodies E99, J533, J415, and J591 prior to March 25, 1999; however, the claims are directed to a genus of antibodies that bind to PSMA and compete for binding to PSMA with a monoclonal antibody selected from the group consisting of monoclonal antibodies E99, J533, J415, and J591. Accordingly, the scope of the showing is not commensurate in scope with the breadth of claims. Moreover, as explained in further detail in the paragraphs below, the evidence neither establishes reduction to practice of the claimed invention, nor its conception.

Essentially for the same reasons that claims 69-74, 76-79, 124-127, 129, 130, 137-148, 150-168, 170-172, 186, and 190 have been rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure, it is submitted that the showing by the declaration is insufficient to establish reduction to practice prior to the

effective date of the reference, or to establish conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application.

M.P.E.P. § 715.02 states:

> Even if applicant's 37 CFR 1.131 affidavit is not fully commensurate with the rejected claim, the applicant can still overcome the rejection by showing that the differences between the claimed invention and the showing under 37 CFR 1.131 would have been obvious to one of ordinary skill in the art, in view of applicant's 37 CFR 1.131 evidence, prior to the effective date of the reference(s) or the activity. Such evidence is sufficient because applicant's possession of what is shown carries with it possession of variations and adaptations which would have been obvious, at the same time, to one of ordinary skill in the art. **However, the affidavit or declaration showing must still establish possession of the invention (i.e., the basic inventive concept)** [emboldened for emphasis] and not just of what one reference (in a combination of applied references) happens to show, if that reference does not itself teach the basic inventive concept. *In re Spiller*, 500 F.2d 1170, 182 USPQ 614 (CCPA 1974).

Again, the breadth of the showing by the declaration is not commensurate with the scope of the claims, which are more broadly directed to any of a genus of antibodies that binds to PSMA and competes for binding to PSMA with a monoclonal antibody selected from the group consisting of monoclonal antibodies E99, J533, J415, and J591.

M.P.E.P. § 715.02 states:

> Where generic claims have been rejected on a reference or activity which discloses a species not antedated by the affidavit or declaration, the rejection will not ordinarily be withdrawn, subject to the rules set forth below, unless the applicant is able to establish that he or she was in possession of the generic invention prior to the effective date of the reference or activity.

There appears no disclosure by the declaration of any factual evidence that Applicant contemplated the generic concept of the invention. Although the declaration discloses antibodies other than monoclonal antibodies E99, J533, J415, and J591, it does not disclose which, if any, compete for binding with PSMA with any one of monoclonal antibodies E99, J533, J415, and J591, and there appears no express reference in any of the evidentiary documents to any antibody that is capable of competing for binding to PSMA with any of these four antibodies.

Furthermore, because the declaration discloses a relatively larger plurality of monoclonal antibodies, which were produced by Applicant, and not just the plurality of the four monoclonal antibodies to which the claims are specifically directed, why then would the differences between the claimed invention and the showing under 37 C.F.R. § 1.131 have been obvious to one of

ordinary skill in the art, in view of the declaratory evidence? Why would the artisan of ordinary skill have selected only antibodies that compete for binding to PSMA with any one of monoclonal antibodies E99, J533, J415, and J591, but not antibodies competing with any of the others? The reason is not immediately apparent; and Applicant has not offered any explanation as to why the declaratory evidence would make obvious any antibody that binds to PSMA and competes for binding to PSMA with any one of the particular monoclonal antibodies to which the claims are directed, but not any of the others.

But for whatever reason, the claims are directed to only antibodies that compete for binding to monoclonal antibodies E99, J533, J415, and J591. The declaratory evidence establishes Applicant's reduction to practice, prior to the date of the reference, of only those monoclonal antibodies; it does not establish a reduction to practice of any antibody that competes for binding to PSMA with any one of these particular four monoclonal antibodies. Moreover, even were the evidence arguably deemed to establish Applicant's possession of the generic concept of the invention, it does not establish Applicant's prior possession of the *particular* species of antibodies, which are disclosed by the reference. The reference describes with particularity 35 antibodies that bind to PSMA; see, e.g., Table 2, which lists 32 of these antibodies, including a large number that bind to the extracellular domain of PSMA (i.e., amino acids 44-750 of the amino acid sequence of the full-length protein, as disclosed therein).

M.P.E.P. § 2131.02 states:

> "A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus." The species in that case will anticipate the genus. *In re Slayter*, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); *In re Gosteli*, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989).

Absent a showing of any difference, it is submitted that the reference discloses a species of antibody falling within the claimed genus of antibodies that bind to PSMA and compete for binding to PSMA with any one of monoclonal antibodies E99, J533, J415, and J591. As explained in the preceding Office action, this position is considered reasonable.

The declaration shows no objective evidence supporting any assertion that Applicant had reduced to practice any of the particular embodiments of the claimed invention that are disclosed by the reference.

M.P.E.P. § 715.03 states:

> [A] reference or activity which discloses several species of a claimed genus can be overcome directly under 37 CFR 1.131 only by a showing that the applicant completed, prior to the date of the reference or activity, all of the species shown in the reference. *In re Stempel*, 241 F.2d 755, 113 USPQ 77 (CCPA 1957).
>
> Proof of prior completion of a species different from the species of the reference or activity will be sufficient to overcome a reference indirectly under 37 CFR 1.131 *if the species shown in the reference or activity would have been obvious in view of the species shown to have been made by the applicant* [italicized for emphasis]. *In re Clarke*, 356 F.2d 987, 148 USPQ 665 (CCPA 1966); *In re Plumb*, 470 F.2d 1403, 176 USPQ 323 (CCPA 1973); *In re Hostettler*, 356 F.2d 562, 148 USPQ 514 (CCPA 1966).

There appears no reason why any one of the antibodies shown by the reference, which is deemed indistinguishable from the claimed antibody, would have been obvious in view of the showing under 37 C.F.R. § 1.131.

Even if the declaratory evidence arguably shows that Applicant contemplated a genus of antibodies that bind to PSMA and compete for binding to PSMA with any one of monoclonal antibodies E99, J533, J415, and J591, the mere contemplation of such a genus does not provide factual evidence of the conception of the species disclosed by the reference; and conception of the invention prior to the effective date of the reference is not sufficient, unless coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application.

However, diligence need not be considered unless conception of the invention prior to the effective date is clearly established, since diligence comes into question only after prior conception is established. See *Ex parte Kantor*, 177 USPQ 455 (Bd. App. 1958); MPEP § 715.07(a).

Even so, it appears that the declaration provides no showing of due diligence before the date of the prior art publication to a subsequent reduction to practice of genus, nor of each of species disclosed by the reference.

Finally, because claims 69-71, 77-80, 125, 126, 129, 130, 136-140, 144, 150, 152-154, 156-161, 164, 165, 171-173, 186, and 190 have been rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure, the

effective filing date of rejected claims is deemed the filing date of the instant application, namely July 20, 1999.

As explained, to receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the declaration by Dr. Bander is insufficient to antedate U.S. Patent No. 6,962,981 B1 (Murphy et al.), which for these reasons is still properly considered prior art under 35 U.S.C. § 102(e).

16. The rejection of claims 69, 77-80, 125-127, 129, 130, 136, 137, 139-141, 147, 150-155, 159, 171-173, 186, and 190 under 35 U.S.C. 102(b), as being anticipated by U.S. Patent No. 5,538,866 A (of record; cited by Applicant), as evidenced by George et al. (*Circulation.* 1998; **97**: 900-906) and Liu et al. (*Cancer Res.* 1998 Sep 15; **58**: 4055-4060) (of record; cited by Applicant), is maintained.

Beginning at page 28 of the amendment filed July 19, 2007, Applicant has traversed the propriety of this ground of rejection.

Applicant's argument has been carefully considered but not found persuasive for the following reasons:

To begin, Applicant has remarked that a rejection over this reference had already been made and overcome during prosecution.

In reply, as explained in the preceding Office action[9]:

> Notably, this reference was previously applied earlier in the prosecution of this application as prior art in a rejection under 35 U.S.C. § 102(e) of then pending claims, which were directed to antibodies or antigen binding portions thereof that bind to the extracellular domain of PSMA. Applicant subsequently amended the claims, so as to be directed to antibodies or antigen binding portions thereof that bind to the epitope recognized by any one of monoclonal antibodies

[9] See Footnote #7 at page 38.

> J591, J415, J533, and E99, arguing the prior art does not teach each and every element of the claims, as Israeli et al. does not teach or suggest antibodies that bind to the specific epitopes recited in the claims. As the present claims are not so limited, and are instead directed to any antibody or antigen binding portion thereof capable of competing for binding to PSMA with any one of a J591, a J415, a J533, and an E99 monoclonal antibody, Applicant's recorded argument in traversal of the rejection of the prior claims as being anticipated by Israeli et al. is presently immaterial.

In addition, Applicant has argued that there is only the mere possibility that antibodies disclosed by the prior art compete for binding to PSMA with a monoclonal antibody selected from the group consisting of monoclonal antibodies J591, J415, J533, and E99, but that is not necessarily so.

The Examiner disagrees with this assertion for the following reasons:

First, U.S. Patent No. 5,538,866 A (Israeli et al.) teaches polyclonal antibodies that bind to the extracellular domain of PSMA. Although Israeli et al. does not expressly teach that the polyclonal antibodies compete for binding with one of monoclonal antibodies J591, J415, J533, and E99, polyclonal antibodies are a *polyclonal* mixture of different antibodies produced by several distinct clones of B lymphocytes; these different antibodies specifically bind to a single antigen, but do so by recognizing any of a variety of different "antigenic determinants" (i.e., *epitopes*) of the antigen. Polyclonal antibodies raised against PSMA bind a plurality of epitopes of PSMA. This plurality of epitopes includes those to which one or more of monoclonal antibodies J591, J415, J533, and E99 bind. Two antibodies cannot occupy the same space. Therefore, because the polyclonal antibodies bind to the same epitope(s) of PSMA as any one of these monoclonal antibodies, they necessarily compete with that monoclonal antibody. Depending upon different physiochemical factors that determine their binding affinity and the stability of the resultant complex, polyclonal antibodies "compete" more or less strongly with one of the monoclonal antibody for binding to PSMA, as compared to some other antibody perhaps, but it nonetheless is fully expected to do so.

Secondly, because the requisite degree to which the claimed antibody "competes" for binding to PSMA is not recited in the claim and cannot be ascertained from a reading of the specification, the claims are broadly but reasonably interpreted to encompass any antibody that binds to PSMA and is capable of inhibiting the binding of one of monoclonal antibodies J591,

J415, J533, and E99. The antibody need not abrogate binding of the monoclonal antibody to PSMA, but must only partially block or interfere with its binding to some measurable extent.

As evidenced by George et al. (cited *supra*), even an antibody that binds to a different epitope of an antigen measurably "competes" for binding to the antigen with another antibody. Moreover, at a high enough concentration, or under certain conditions, *any* antibody, including an antibody that binds to a different epitope of an antigen than the epitope recognized by another antibody that binds the antigen is expected to "compete" for binding to the antigen with the other antibody.

Neither the claims nor the disclosure delineate the conditions under which the determination is made that the antibody "competes" with one of monoclonal antibodies J591, J415, J533, and E99. Furthermore, as thoroughly explained in the rejections of claims under 35 U.S.C. § 112, first and second paragraphs, the claims do not define the extent to which the claimed antibody or antigen binding fragment "competes", nor do they define the methodology by which such a determination is made, and under what conditions.

Accordingly, although Israeli et al. does not expressly teach any of the disclosed monoclonal antibodies "compete" for binding to PSMA with monoclonal antibodies J591, J415, J533, and/or E99, there is a reasonable presumption that one or more of the particularly disclosed monoclonal antibodies bind the same or an overlapping epitope of PSMA as those recognized by one or more of monoclonal antibodies J591, J415, J533, and E99, especially since these antibodies bind to antigenic determinants of the same extracellular domain of PSMA to which the latter antibodies bind (see, e.g., Figure 20).

Therefore, absent a showing of any difference, the polyclonal or monoclonal antibodies disclosed by Israeli et al. are deemed the same as the claimed antibodies and antigen binding fragments thereof.

As previously noted, the Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the antibodies and antigen binding fragments thereof. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the antibody disclosed by the prior art differs from the

claimed antibody. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Beginning at page 29 of the amendment filed July 19, 2007, Applicant has referenced Holmes (*Expert Opin. Investig. Drugs.* 2001 Mar; **10** (3): 511-519), arguing that polyclonal antibodies produced using an immunogen comprised of one of three particular peptide fragments of PSMA and a carrier protein (i.e., KLH) did not bind to intact PSMA.

In response to this argument, the polyclonal antibodies disclosed by the prior art are *not* limited to antibodies produced using the particular immunogen described by Holmes. Israeli et al. describes the polyclonal and monoclonal antibodies as including, but not limited to those directed to a peptide of the PSM antigen selected from Asp-Glu-Leu-Lys-Ala-Glu (SEQ ID No. 35), Asn-Glu-Asp-Gly-Asn-Glu (SEQ ID No. 36), and Lys-Ser-Pro-Asp-Glu-Gly (SEQ ID No. 37); see, e.g., column 6, lines 48-52. Notably, in addition to these three peptide sequences, Israeli discloses the amino acid sequences of at least 9 other peptides, which are fragments of the full-length antigen; see, e.g., columns 16 and 17; and SEQ ID NOs: 3-12, 31, and 34-38. Moreover, Israeli et al. describes the antibodies as inclusive of antibodies produced using the purified, intact antigen; see, e.g., column 6, lines 38-47.

In addition, despite the anecdotal disclosure by Holmes of a peptide that is incapable of eliciting the production of an antibody that binds to the intact protein, it is aptly noted that it was well within the knowledge and skill of the artisan at the time of the invention, and at the time of the disclosure by the prior art, to produce an antibody that binds to an intact antigen using either the intact antigen or only a fragment of the antigen. For example, given the disclosure by the prior art, it would have been immediately appreciated that such polyclonal antibodies could readily be generated using the intact PSM antigen as an immunogen, or perhaps just a substantial portion thereof, such as the extracellular domain of the antigen[10]. Alternatively, as evidenced by Shinnick et al. (*J. Invest. Dermatol.* 1984 Jul; **83** (1 Suppl.): 112s-115s), the skilled artisan could have, as a matter of routine and conventional experimentation, produced a synthetic peptide for use as an immunogen to elicit antibodies that can react with the full-length protein containing that peptide, where such antibodies are directed against a specific region of the protein

containing that peptide, which is chosen in advance by the investigator to produce an antibody having a predetermined specificity; see entire document (e.g., the abstract)[11].

Beginning at page 30 of the amendment Applicant has argued that the antibodies of the prior art are "at best described as a genus of antibodies that bind PSMA, and as such they do not anticipate the species of antibodies of the claimed methods" (paragraph 2).

In reply, the claims are not directed to any one species of antibody, but are *generic*. Moreover, the claims are directed to a genus of antibodies that bind to PSMA, albeit a genus that is limited to antibodies that compete for binding to PSMA with a monoclonal antibody selected from the monoclonal antibodies of which Applicant was in possession at the time the application was filed (i.e., one of monoclonal antibodies J591, J415, J533, and E99). Similarly, the antibodies described by the prior art are antibodies that bind to PSMA. More particularly, the antibodies described by the prior art are antibodies that bind to the extracellular domain of PSMA, as opposed to any antibody that binds any domain of PSMA, which under some undefined conditions, is capable of competing for binding to PSMA with one of Applicant's four monoclonal antibodies. The antibodies described by the prior art are thus in a sense more limited than the antibodies to which the claims are directed, since, as explained, under certain conditions, any antibody that binds to PSMA is capable of "competing" with another antibody that binds to this same antigen, such as one of monoclonal antibodies J591, J415, J533, and E99.

In further reply to this line of argument, although the claims are not limited to antibodies that bind to the same epitope or domain of PSMA as any of monoclonal antibodies J591, J415, J533, and E99, each of these monoclonal antibodies binds to the extracellular domain of PSMA, and so do the antibodies disclosed by the prior art. For this reason, it has been submitted that there is a reasonable expectation that at least one of the 30 or more different monoclonal antibodies described by Israeli et al. binds to the same epitope as one or more of Applicant's

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[10] Notably, Israeli et al. discloses, "generation of polyclonal and monoclonal antibodies against highly antigenic peptide domains of the PSM antigen" is presently underway; see, e.g., column 3, lines 13-22.

[11] In addition, as Applicant has noted, Holmes (*supra*) discloses that the use of slightly longer peptides, as described by Murphy et al. (reference #19), might overcome the problem with using amino acids 63-68, 132-137, or 482-487 as an immunogen to produce antibodies reactive against the intact antigen; see page 513, column 1. Notably, suggesting that doing so is but a matter of routine experimentation, Holmes further discloses that Murphy et al. describes the production of the monoclonal antibody 3F5.4G6, which reacts with the extracellular domain of the intact antigen; this antibody was produced by immunizing mice with a peptide consisting of amino acids 716-723 of PSMA.

monoclonal antibodies, and if so, competes for binding to PSMA with those monoclonal antibodies.

The antibodies disclosed by the prior art are either encompassed by the claims, or they are not, i.e., the antibodies described by Israeli either compete for binding to PSMA with one of monoclonal antibodies J591, J415, J533, and E99, or they do not.

The prior art cannot have known that the antibodies disclosed therein bind to the same epitopes as any one of Applicant's *novel* monoclonal antibodies, so it should be of little consequence that the art is silent as to whether or not their antibodies are capable of competing for binding to PSMA with one of monoclonal antibodies J591, J415, J533, and E99. That property of the antibodies of the prior art to do so, or not to do so, is inherent; moreover, it is a matter of fact that is determinable, but as has been explained previously, the Office does not have the facilities for establishing that there are material, structural and/or functional differences between the products of the prior art and the products that are encompassed by the claims. Thus it is Applicant's burden to prove that the antibody disclosed by the prior art differs from the claimed antibody.

As to inherency, the Court has noted that "[u]nder the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *Mehl/Biophile Int'l Corp. v. Miligraum*, 192 F.2d 1362, 1366, 52 USPQ2d 1303, 1305 (Fed. Cir. 1999) (citations omitted).

In addition, granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. See *In re Baxter Travenol Labs,* 21 USPQ2d 1281 (Fed. Cir. 1991). See also: *In re Wiseman,* 201 USPQ 658 (CCPA 1979); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1575 (Fed. Cir. 1990); and *Bristol-Myers Squibb Company v. Ben Venue Laboratories*, 58 USPQ2d 1508 (CAFC 2001). See M.P.E.P. § 2145.

As such, although Applicant's arguments have been carefully considered, the Office's position is founded in scientific reasoning, factual evidence, and an analysis of legal precedence, and given the fact that Israeli et al. disclosed polyclonal antibodies, as well as at least 30 different monoclonal antibodies that bind to the extracellular domain of PSMA, it is reasonably

concluded *in the absence of factual evidence indicating otherwise* that the prior art's disclosure is anticipatory of the claimed invention.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. The rejection of claims 70, 71, 160, 161, 164, and 165 under 35 U.S.C. 103(a), as being unpatentable over U.S. Patent No. 5,538,866 A (of record; cited by Applicant), as evidenced by George et al. (*Circulation*. 1998; **97**: 900-906), is maintained.

At page 32 of the amendment filed July 19, 2007, Applicant has traversed the propriety of this ground of rejection, arguing that the prior art (i.e., Israeli et al.) neither teaches nor suggests the claimed invention for the same reasons that have already been discussed in traversing the rejection of claims under 35 U.S.C. § 102.

Applicant's argument has been carefully considered but not found persuasive for those same reasons that are presented above in responding to Applicant's traversal of the ground of rejection of claims 69, 77-80, 125-127, 129, 130, 136, 137, 139-141, 147, 150-155, 159, 171-173, 186, and 190 under 35 U.S.C. § 102(b).

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference

claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. The provisional rejection of claims 69-71, 77-80, 124-127, 129, 130, 136-155, 159-161, 164, 165, 171-173, 186, and 190 on the ground of nonstatutory obviousness-type double patenting, as being unpatentable over claims 55-59 and 172-316 of copending Application No. 10/449,379, is maintained.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

At page 33 of the amendment filed July 19, 2007, Applicant has remarked that this issue be addressed upon an indication of allowance in either of the applications of issue.

Applicant's remark has been carefully considered; this ground of provisional rejection shall however be maintained until remedied.

Furthermore, substantive issues are not ordinarily held in abeyance. Concerning a fully responsive reply to a non-final Office action, it is noted that 37 C.F.R. § 1.111(b) states:

> In order to be entitled to reconsideration or further examination, the applicant or patent owner must reply to the Office action. The reply by the applicant or patent owner must be reduced to a writing which distinctly and specifically points out the supposed errors in the examiner 's action and must reply to every ground of objection and rejection in the prior Office action. The reply must present arguments pointing out the specific distinctions believed to render the claims,

> including any newly presented claims, patentable over any applied references. If the reply is with respect to an application, a request may be made that objections or requirements as to form not necessary to further consideration of the claims be held in abeyance until allowable subject matter is indicated. The applicant 's or patent owner 's reply must appear throughout to be a *bona fide* attempt to advance the application or the reexamination proceeding to final action. A general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references does not comply with the requirements of this section [underling added for emphasis].

The issue at hand is not a matter of form, but rather the substantive issue of sufficiency, or lack thereof, of the specification to satisfy the requirements set forth under 35 U.S.C. § 112, first paragraph.

An amendment which does not comply with the provisions of 37 C.F.R. 1.121(b), (c), (d), and (h) may be held not fully responsive. See M.P.E. P. § 714.02.

Accordingly, Applicant should either traverse the propriety of this ground of rejection, or remedy the issue by appropriately amending the claims of this or the copending application, or if appropriate file a terminal disclaimer.

21. Claims 69-71, 77-80, 127, 129, 130, 136, 139, 140, 151, 159-161, and 190 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-61 of copending Application No. 11/219,563, is maintained.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

At page 33 of the amendment filed July 19, 2007, Applicant has remarked that this issue be addressed upon an indication of allowance in either of the applications of issue.

Applicant's remark has been carefully considered; this ground of provisional rejection shall however be maintained until remedied.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

22. Claim 156 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

Claim 156 is directed to "an endogenous host immune function that is therapeutically effective against prostate cancer".

At page 12 of the amendment filed July 19, 2007, Applicant has remarked that support for the amendment to the claims is found throughout the specification, as filed, including, e.g., page 19, Table 1.

It was previously noted with particular regard to claim 156, which is directed to the method of claim 69, 125, 126, or 127, wherein the antibody or antigen binding portion thereof is effective to initiate an endogenous host immune function, most murine monoclonal antibodies, which are administered to humans, are effective to initiate an immune response against the antibodies. However, this property of the murine antibodies is generally recognized as a limitation to the effective treatment of humans, as the resultant immune response preclude repeated administrations that will likely cause undesired and potentially harmful side-effects (e.g., immune hypersensitivity, and perhaps anaphylactic shock). Therefore, it was previously submitted that the disclosure does not reasonably enable the use of the claimed invention, as it would not be practiced effectively using antibodies capable of initiating any and all types of endogenous host immune functions, but perhaps only such immune responses that are therapeutically efficacious against prostate cancer cells, such as ADCC or CMCC. Accordingly, Applicant has amended claim 156 to recite, "that is therapeutically effective".

It does not appear however that there is support in the specification, including the claims, as filed, for the recitation by claim 156 of such a limitation.

The claim, as amended, is directed to a subgenus of "therapeutically effective" endogenous host immune functions that presumably excludes, for example, human anti-mouse antibody (HAMA) response, which would are not expected to be therapeutically effective. The specification appears to describe therapeutically effective endogenous host immune functions to include complement-mediated cellular cytotoxicity and antibody-dependent cellular cytotoxicity; but it does not appear to describe the subgenus of "endogenous host immune functions" to which the claim is now directed. For example, the specification discloses: "Where the biological agents are used alone to kill or ablate prostate epithelial cells, such killing or ablation can be effected by initiating endogenous host immune functions, such as complement-mediated or

antibody-dependent cellular cytotoxicity"; but otherwise it does not describe identifying attributes of the "therapeutically effective" or "therapeutically *ineffective*" endogenous host immune function. Moreover, it does not appear to describe endogenous host immune functions as inclusive of any particularly species (e.g., HAMA), which are not therapeutically effective.

Therefore, Applicant is reminded that it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith*, 173 USPQ 679, 683 (CCPA 1972).

Furthermore, inasmuch as the record might suggest Applicant's intent to exclude therapeutically *ineffective* endogenous host immune functions, such as HAMA, from the scope of the claims, it appears that Applicant would add the implied exclusion of certain elements, but the permissible inclusion of all other elements not so impliedly excluded. It is submitted that this clearly illustrates that such amendments have in fact introduced new concepts.

M.P.E.P. § 2173.05(i) states on the basis of various case law, including *In re Johnson:* "Any negative limitation or exclusionary proviso must have basis in the original disclosure." In deciding *In re Johnson*, the Court decided that since appellant had described the genus *and* the species, which appellant had deliberately excluded from the claimed subject matter by the proviso exclusion of those species, appellant had not created "an artificial genus" (or an inadequately described subgenus), because the specification, having described the whole, must necessarily have described the part remaining after the proviso exclusion of the species. In this instance, however, Applicant's disclosure does not include a description of the one or more species Applicant wishes to exclude. In deciding *Ex parte Grasselli*, 231 USPQ 393 (BPAI 1983), the Court decided that such an attempt to exclude species of a genus, which had not been described, introduces new matter into the specification as originally filed. See also *In re Welstead*, 59 CCPA 1105, 463 F.2d 1110, 174 USPQ 449 (1972); and *In re Lukach*, 58 CCPA 1233, 442 F.2d 967, 169 USPQ 795 (1971).

Conclusion

23. No claim is allowed.

24. The art made of record and not relied upon is considered pertinent to Applicant's disclosure. Russell et al. (*Cancer Immunol. Immunother.* 2004 May; **53** (5): 411-421) teaches an immunoconjugate comprised of mouse monoclonal antibody J591 and a cytotoxic moiety, namely melittin-like peptide 101 inhibited tumors in mice, whereas the unconjugated antibody was largely ineffective; see entire document (e.g., page 417, column 2, through page 419, column 1.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/
Stephen L. Rawlings, Ph.D.
Primary Examiner
Art Unit 1643

slr
October 14, 2007